Inventor(s): Elliot Ehrich, Daniel Deaver, Robert Clarke and Michael M. Lipp

Attorney's Docket No.: 2685.3002

TROSPIUM CONTAINING COMPOSITIONS

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Application No. 10/392,333, filed March 19, 2003, which claims the benefit of U.S. Provisional Application Nos. 60/366,479, 60/366449, 60/354354, 60/366487 and 60/366440, filed on March 20, 2002. The entire teachings of the above application(s) are incorporated herein by reference.

BACKGROUND OF THE INVENTION

It is known from the prior art that .beta.-mimetics and anticholinergics can successfully be used as bronchospasmolytics for the treatment of obstructive respiratory ailments, such as, e.g., asthma. Substances with .β.-sympathomimetic effectiveness, such as, e.g., the active substance formoterol, also known from the prior art, can, however, be associated with undesirable side-effects when administered to humans. There remains a need for formulations and methods for administering combinations of beta-mimetics and anticholingerics in a formulation that provides long lasting broncoprotection in a patient while minimizing undesireable side effects.

SUMMARY OF THE INVENTION

The invention relates to a method for treating a disease characterized by a constrictive airway comprising administering to a patient in need thereof via inhalation a pharmaceutical composition comprising trospium (spiro [8-

azaniabicyclo[3.2.1] octane-8,1'-pyrrolidinium], 3-4[hydroxydiphenylacetyl)oxy]-chloride (1α, 3β, 5α)) wherein said patient achieves an effective therapy for at least 10 hours. The trospium composition is preferably a particulate formulation useful for administration via a dry powder inhaler. In a preferred embodiment, the composition further comprises a second active agent, such as a beta-2 agonist. A particularly preferred second active agent is formoterol, wherein the trospium, formoterol composition is manufactured by spray drying a mixture comprising trospium and formoterol.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1a and 1b show the percent (%) baseline PenH over time following treatment at varying doses of aqueous Ipatropium bromide (IpBr) (Fig 1a) and aqueous Trospium Chloride (TrCl) (Fig.1b).

Figure 2 shows the percent (%) baseline PenH over time following treatment at equal nominal doses of aqueous IpBr or aqueous TrCl.

Figure 3 shows the percent (%) baseline PenH over time following treatment with aqueous TrCl or particle formulations TrCl at a nominal dose of 1mcg for each formulation.

DETAILED DESCRIPTION OF THE INVENTION

The invention is based upon the discovery that trospium, when administered via inhalation results in surprisingly long acting formulation. Thus, a single daily administration, or twice daily administration, of trospium can be used to achieve and maintain relief of such diseases as chronic pulmonary disorder.

Thus, in one embodiment, the invention relates to a method for treating a disease characterized by a constrictive airway comprising administering to a patient in need thereof via inhalation a pharmaceutical composition comprising trospium, wherein said patient achieves an effective therapy for at least about 10 hours, preferably at least about 15 hours, more preferably at least about 24 hours.

Diseases that can be treated by the present invention include diseases indicated for trospium. For example, patients suffering from asthma, chronic obstructive pulmonary disease (COPD), restriction of the bronchial airways, or

bladder diseases, such as urinary incontinence, can be treated by practicing the invention

The invention further relates to pharmaceutical compositions for use in the present methods. The compositions comprise a therapeutically effective amount of trospium. A therapeutically effective amount includes an amount which, alone or in combination with one or more other active agents, can control, decrease, inhibit, ameliorate, prevent or otherwise affect one or more symptoms of the disease(s) or condition(s) to be treated.

Typically, the dose of the active agent to be delivered is related to the efficiency of the inhalation device to deliver the active agent to the patient and the bioavailability of the active agent upon delivery. The preferred human dose of trospium is about 50 to 1200 micrograms per inhalation nominal dose delivered to lung, and even more preferably about 200-800 micrograms per inhalation nominal dose delivered to lung.

The composition can be administered via a number of different pulmonary routes, which can impact the form of the composition. In one embodiment, the composition comprises an aqueous solution or suspension of trospium or a trospium salt, such as a hydrochloride. In another embodiment, the composition comprises a particulate formulation comprising trospium, such as a dry particulate formulation of trospium to be administered with a dry powder inhaler. In this context, a "dry powder" contains less than about 5% by weight of water, based on the total solids of the composition.

The trospium formulations can, in one embodiment, comprises micronized trospium. However, it is preferred to administer formulations that comprise spray-dried trospium. Preferred formulations are described in, for example, United States Serial No. 10/392,333, which is incorporated herein by reference. Such formulations have superior deposition properties. That is, preferred formulations are characterized by a tap density of less than 0.4 g/cm^3, preferably less than 0.3 g/cm^3, more preferably less than about 0.2 g/cm^3, more preferably less than about 0.1 g/cm^3, or even less than about 0.05 g/cm^3. Further the formulation has a mass mean aerodynamic diameter of less than 5 microns. A preferred dry particulate formulation is characterized by a fine particle fraction of at least about 50%, wherein

the fine particle fraction is defined as the mass of the composition that possesses an aerodynamic diameter of less than 3.4 microns as determined with an 8 Stage Anderson Cascade Impactor, used according to manufacturer's instructions.

Preferred compositions further comprise an amino acid. Preferred amino acids are hydrophobic amino acids, such as leucine, isoleucine, alanine, valine and phenylalanine, for example. The preferred amino acid is leucine. The amino acid can advantageously be added in amount of at least about 10% by weight of the total composition. In one embodiment, the amino acid is at least about 40%, preferably at least about 50%, more preferably at least about 70% by weight of total composition.

The compositions can further advantageously contain or comprise one or more phospholipids or combinations thereof. Suitable phospholipids include phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof. A particularly preferred phospholipid is dipalmitoylphosphatidylcholine (DPPC). The phospholipid can be advantageously added in an amount between about 1% and 90%, preferably between about 1 and 70%, more preferably between about 1% and 30%, such as between about 5 and 10% by weight of the total composition. The weight of the composition, as defined herein is, of course, non-inclusive of water and residula solvents or volatiles.

The composition can comprise additional optional excipients, such as sugars, polysaccharides, lactose, salts, buffers, lipids, cholesterol, fatty acids, ancd combinations thereof.

As described above, the formulation contains trospium. The formulation can consist of or consist essentially of trospium or a salt thereof. In another embodiment, the formulations can contain less than about 90%, 80%, 70%, 60%, 50%, 40%, 30% or 20% by weight trospium. In a preferred embodiment, the formulation contains less than about 10% by weight of trospium. In another preferred embodiment, the formulations contain about 1% to 25% by weight trospium and even more preferably about 4% to16% by weight tropsium.

A preferred composition consists essentially of a formulation having about 5% by weight trospium hydrochloride; between about 5 and 10% by weight of phospholipid and between about 85 and 90% by weight of leucine.

In one embodiment, the method further comprises the administration of a second active agent. Preferred drugs for coadministration are described in more detail in US Serial No. 10/392,333 incorporated herein by reference. A preferred active agent is a beta-2 agonist, with formoterol and salmeterol being preferred.

The second active agent can be administered simultaneously or separately from the trospium formulation. Where the second agent is administered separately, it can be administered via inhalation or other route, including without limitation enteral, such as oral, and parenteral administrations, such as by injection.

Simultaneous administration via inhalation is, however, preferred. The second active agent is advantageously incorporated into the trospium formulation. This can be advantageously accomplished by spray drying for example, a trospium and formoterol containing mixture. These combination formulations can be those described above wherein preferred doses of formoterol are in the range of 1 to 15 micrograms per inhalation nominal dose delivered to lung, and more preferably 2.5 to 5 micrograms per inhalation nominal dose delivered to the lung. Loads of formoterol in spray dried particles are preferably from 0.01% to 2% and more preferably from about 0.05% to 0.4%. Ratios of trospium to formoterol in a formulation are preferably in the range from about 10/1 to 1000/1 and more preferably from about 40/1 to 320/1.

In a preferred embodiment, the composition comprises a spray dried formulation comprising trospium, formoterol, leucine and, optionally, at least one phospholipid, the formulation having a low tap density, as described herein, and a mean aerodynamic diameter of between about 1 and 3 microns, and/or with a fine particle fraction of at least about 50%.

The formulation is administered in an amount to provide the desired dose of the active agent. Inherent in pulmonary delivery is loss of some portion of the drug due to loss of some powder in the inhaler, expiration of the drug by the patient, and other losses. Thus, the amount of formulation loaded into the inhaler device can depend upon the efficiency of the device for the formulation. This amount can be calculated using methods known to the person of ordinary skill in the art.

In accordance with the above, the invention also provides a pharmaceutical kit comprising one or more compositions or formulations in separate unit dosage

forms, said forms being suitable for administration of the drugs in effective amounts. Such a kit can comprise one or more inhalation devices. For example, the kit may comprise one or more dry powder inhalation (DPI) devices adapted to deliver dry powder from a capsule, together with capsules containing a dry powder. In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof formulations described herein. In a further example, the kit may comprise a metered dose inhaler (MDI) containing an aerosol in a propellant. In yet another example, the kit may comprise a nebulizer inhalation device for delivering aerosolized compositions described herein.

Dry powder formulations as described herein may be delivered using any suitable dry powder inhaler (DPI), i.e., an inhaler device that utilizes the patient's inhaled breath as a vehicle to transport the dry powder drug to the lungs. Examples of suitable inhalers include those of United States Patent Publication No. 2003/0150453, and in PCT publication WO 02/083220 which is hereby incorporated by reference. Other examples include Inhale Therapeutic Systems' dry powder inhalation devices as described in Patton, J. S., et al., U.S. Pat. No. 5,458,135, Oct. 17, 1995; Smith, A. E., et al., U.S. Pat. No. 5,740,794, Apr. 21, 1998; and in Smith, A. E., et. al., U.S. Pat. No. 5,785,049, Jul. 28, 1998, herein incorporated by reference. When administered using a device of this type, the powdered medicament is contained in a receptacle having a puncturable lid or other access surface, preferably a blister package or cartridge, where the receptacle may contain a single dosage unit or multiple dosage units. Convenient methods for filling large numbers of cavities (i.e., unit dose packages) with metered doses of dry powder medicament are described, e.g., in Parks, D. J., et al., International Patent Publication WO 97/41031, Nov. 6, 1997, incorporated herein by reference.

Other dry powder dispersion devices for pulmonary administration of dry powders include those described, for example, in Newell, R. E., et al, European Patent No. EP 129985, Sep. 7, 1988; in Hodson, P. D., et al., European Patent No. EP472598, Jul. 3, 1996; in Cocozza, S., et al., European Patent No. EP 467172, Apr. 6, 1994, and in Lloyd, L. J. et al., U.S. Pat. No. 5,522,385, Jun. 4, 1996, incorporated herein by reference. Also suitable for delivering dry powder formulations described herein are inhalation devices such as the Astra-Draco

"TURBUHALER". This type of device is described in detail in Virtanen, R., U.S. Pat. No. 4,668,218, May 26, 1987; in Wetterlin, K., et al., U.S. Pat. No. 4,667,668, May 26, 1987; and in Wetterlin, K., et al., U.S. Pat. No. 4,805,811, Feb. 21, 1989, all of which are incorporated herein by reference. Other suitable devices include dry powder inhalers such as Rotahaler.RTM. (Glaxo), Discus.RTM. (Glaxo), Spiros.TM. inhaler (Dura Pharmaceuticals), and the Spinhaler.RTM. (Fisons). Also suitable are devices which employ the use of a piston to provide air for either entraining powdered medicament, lifting medicament from a carrier screen by passing air through the screen, or mixing air with powder medicament in a mixing chamber with subsequent introduction of the powder to the patient through the mouthpiece of the device, such as described in Mulhauser, P., et al, U.S. Pat. No. 5,388,572, Sept. 30, 1997, incorporated herein by reference.

Formulations described herein may also be delivered using a pressurized, metered dose inhaler (MDI), e.g., the Ventolin.RTM. metered dose inhaler, containing a solution or suspension of drug in a pharmaceutically inert liquid propellant, e.g., a chlorofluorocarbon or fluorocarbon, as described in Laube, et al., U.S. Pat. No. 5,320,094, Jun. 14, 1994, and in Rubsamen, R. M., et al, U.S. Pat. No. 5,672,581 (1994), both incorporated herein by reference.

Alternatively, the formulations described herein may be dissolved or suspended in a solvent, e.g., water or saline, and administered by nebulization. Nebulizers for delivering an aerosolized solution include the AERx.TM. (Aradigm), the Ultravent.RTM. (Mallinkrodt), the Pari LC Plus.TM. or the Pari LC Star.TM. (Pari GmbH, Germany), the DeVilbiss Pulmo-Aide, and the Acorn II (Marquest Medical Products).

Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as

incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis and emphysema, bronchiectasis and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis

EXAMPLES

Example 1

Preparation of Trospium Chloride (TrCl) Particle Formulations

Particle formulations, as listed in Table 1, where prepared by spray drying. Pre-spray drying solutions were prepared as follows. Particle components were dissolved in appropriate solvents to assure solubility. Table 2 lists the mass of each particle component dissolved in each respective solvent. Leucine was dissolved in 300 mL of water. TrCl was subsequently dissolved in the aqueous solution. DPPC and/or DSPC were dissolved in 700 mL of ethanol, to form an organic phase. Both solutions were then heated separately to 50°C.

Phospholipids (dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC)) were obtained from Avanti Polar Lipids, Inc. (Alabaster, AL). TrCl was obtained from Boeringer Ingelheim and leucine was obtained from Spectrum Quality Products, Inc. (Gardena, CA).

The aqueous phase was then static mixed with the organic phase and then spray dried to produce dry powders. A Niro Size 1 Spray Dryer (Niro, Inc., Columbus, MD) was used with two-fluid atomization using nitrogen as the atomization gas at 15 gr/min. Liquid feed at a rate of 60 mL/min was pumped continuously by a peristaltic pump to the atomizer. Dry nitrogen gas (100 kg/hr) was used as the drying medium. Both the inlet and outlet temperatures were measured. The inlet temperature was controlled manually and was established at approximately 115°C. Outlet temperature is determined by such factors as the input temperature and the gas and liquid feed rates, among others. The outlet temperature was about 54°C. A container was tightly attached to a cyclone for collecting the powder product. Yield was determined by comparing final total powder produced and dividing by the total starting solids of 1 gram. Yields for formulations A, B and C were 50%, 64% and 50%, respectively.

Table 1: Formulations

Formulation	Composition (weight percent)
A	Leucine (90%); DPPC (5%); Trospium (5%)
B	Leucine (85%); DPPC (10%); Trospium (5%)
C	Leucine (855); DPPC (5%); DSPC (5%); Trospium (5%)

Table 2: Pre-Spray Drying Solution Composition

Formulation	Ethanol Solution Components 700 ml		Aqueous Solution Components 300ml		
	DPPC	DSPC	Leucine	TrCl	
A	50 mg	--	900 mg	50 mg	
B	100 mg	--	850 mg	50 mg	
C	50 mg	50 mg	850 mg	50 mg	

Example 2

The Fine Particle Fraction (FPF), volumetric median geometric diameter, and actual trospium content of the particles produced in Example 1 were determined.

The content of trospium chloride in the AIR-Trospium formulations was determined via HPLC using a Waters HPLC system equipped with a PDA detector as shown in Table 3. AIR-Trospium formulations were targeted to have a content of 5% trospium chloride.

Table 3. AIR-Trospium content analysis parameters.

Column	Alltech Alltima C18 (250 – 4.6 mm)
Dissolving Solvent	90% MeOH, 10% 0.01 N HCl
Detection Wavelength	265 nm
Injection Volume	10 uL
Flow Rate	1 mL/min
Mobile Phase	60/40 (0.05% TFA in Water / 0.05% TFA in ACN)
Run Time	10 min.
Relative Retention Time	6.0 min.

The volumetric median geometric diameter (VMGD) of the particles was measured using a RODOS dry powder disperser (Sympatec, Princeton, NJ) in conjunction with a HELOS laser diffractometer (Sympatec). Powder was introduced into the RODOS inlet and aerosolized by shear forces generated by a compressed air stream regulated at 1 bar. The aerosol cloud was subsequently drawn into the measuring zone of the HELOS, where it scattered light from a laser beam and produced a Fraunhofer diffraction pattern used to infer the particle size distribution and determine the median value.

Fine Particle Fractions (FPF) below 5.6 and 3.4 microns were obtained via cascade impaction (2-stage system utilizing gravimetric analysis). Capsule loadings of approximately 5 mg were utilized. The AIR-1 inhaler was used for these experiments. A flow rate of 60±1.0 LPM was run for 2 seconds to obtain an overall air volume of 2 L.

Volumetric median geometric diameter, FPF<3.4, FPF<5.6, and actual TrCl content for each of the formulations produced in Example 1 are shown in Table 3 below. The powders produced are respirable, as indicated by the physical characteristics of the powders shown in Table 4.

Table 4: Particle Characterization Data

Formulation	VGMD (microns)	FPF<3.4 microns (%)	FPF<5.6 microns (%)	Actual TrCl Content (%)
A	8.64	58.7	78.6	4.6
B	8.23	55.6	79.9	4.8
C	7.07	53.4	75.4	4.6

Evaluation of Broncoprotection Over Time in a Guinea Pig Model of Airway Bronchoconstriction

The purpose of this study was to establish a dose-response curve for the anti-cholinergic Trospium chloride (TrCl) in a guinea pig model of airway hyperresponsiveness. Ipratropium bromide (IpBr), a similar acting anticholinergic drug currently commercially available for use in the treatment of asthma and COPD, was used as a comparator. Guinea pigs were intratracheally instilled with either dry powder or aqueous TrCl or acqueous IpBr at varying concentrations (1-50 μg for TrCl; 0.1-5.0 μg for IpBr). Changes in airway responsiveness to nebulized methacholine (Mch) (1,000 μg/mL) were measured using a BUXCO non-invasive plethysmography system. Assessment of airway resistance to methacholine was performed prior to treatment (baseline) and at 2, 6, 10, 14, 24 and 42 hours post-treatment with either IpBr or TrCl. The enhanced pause (PenH), a surrogate measure of bronchoconstriction in the BUXCO system, was used as the biomarker of response in this study. An increase in this value indicates increased airway resistance; prevention of this increase in response to methacholine is indicative of bronchoprotection. The Guinea Pig (GP) Mch-induced bronchoconstriction provides a useful model that can differentiate between short- and long-acting bronchodilatory molecules. In addition, this model is a valuable screening tool for formulation comparisons including dry powders and aqueous solutions containing TrCl.

Animals were administered the test compound in a dry powder formulation (or liquid formulation) using an intratracheal insufflation technique with a Penn Century (Philadelphia, PA) insufflation device. Briefly, animals were anesthetized prior to treatment and the tip of the insufflation device is placed into the trachea about 1 cm above the carina. Actuation of the insufflation device delivers an aerosol bolus of the test formulation that deposits throughout the airways and lung parenchyma while avoiding deposition losses in the oropharyngeal region. Respirable liquid aerosols containing bronchodilatory API were delivered using a liquid insufflation device (Penn Century).

The degree and duration of bronchoprotection is evaluated at discrete timepoints in individual animals using a non-invasive BUXCO Whole Body Plethysmography system (BUXCO Electronics, Inc. Sharon, CT). Briefly, a flow transducer detects pressure/volume changes within a whole-body plethysmography chamber, which the BUXCO software subsequently translates into pulmonary function parameters including a surrogate measure of airway resistance referred to as PenH, or "enhanced pause". The lower the PenH value at a given timepoint, the greater the bronchoprotection offered by the API.

Bronchoprotection in individual animals was assessed following challenge with Mch aerosol at discrete timepoints following API treatment compared to a pre-treatment baseline Mch challenge. The Mch challenge protocol at each timepoint consists of three parts: 1) 10 minutes of acclimatization in the whole-body plethysmograph; during this time, the animals typically develop a quiescent breathing pattern and a comfortable posture; 2) A nebulized aerosol of saline (vehicle control) is delivered for 30 seconds and pulmonary function is assessed for 15 minutes; and 3) A nebulized Mch aerosol is delivered for 30 seconds and pulmonary function is assessed for 15 minutes. The 15 minute assessment period following Mch challenge allows observation of the complete timecourse of the baseline bronchoconstrictive response; following Mch challenge, peak PenH values occur between 4 and 9 minutes with a subsequent return to pre-challenge PenH levels by 15 minutes post-challenge. At each individual timepoint, the degree of bronchoprotection was measured as the mean peak PenH values (4-9 minutes).

Data from any individual test animal was excluded if any of the following conditions are met: 1) Rarely, during insufflation, the insufflation needle damages the trachea causing an injury that causes PenH to be elevated ("IJ"); 2) if an animal never exhibits any bronchoprotection from bronchoprovocative challenge, it is assumed dosing was missed (DM); 3) At any point during the study prior to recovery (≥ 24 hours), the animal expires ("EX"); 4) Following treatment, the animal has a response to methacholine much greater than that measured prior to treatment at any timepoint (> 200% of the Pre-Treatment bronchoconstrictive response; "Hyperresponder, HR"); 5) At a timepoint where no further bronchoprotective effects would be expected (>> 24 hours), an animal exhibits little or no response to methacholine (<40% of original response; "Non-Responder (NR)"). In addition, animals that provide little or no initial response to nebulized methacholine during baseline assessment are excluded from the study.

Trospium Chloride Dose-Response Assessment

Guinea pigs were delivered aqueous trospium chloride at increasing doses (range = 1.0-50.0 μg TrCl) using the Penn Century liquid insufflation device. Bronchoprotection from Mch-induced bronchoconstriction was assessed at 2, 6, 10, 14, and 24 hours following TrCl treatment and compared to the pre-TrCl treatment baseline Mch response. Aqueous ipratropium bromide (IpBr) was used as a control comparator at multiple doses (range = 0.1-5.0 mcg). Doses of each compound are shown in Table 5.

Dose (mcg)	IpBr	TrCl
0.1	X	
0.5	X	
1.0	X	X
2.0		X
3.5		X
5.0	X	X
10.0		X
50.0		X

Table 5.

Figures 1a and 1b show the percent (%) baseline PenH over time following treatment at varying doses of aqueous IpBr (Fig 1a) and aqueous TrCl (Fig.1b). Each line represents a group of animals treated with a single dose of IpBr or TrCl. Each data point within the line represents the mean % baseline PenH of the treatment group (assessed as the peak PenH response from minutes 4-9 following Mch challenge at each timepoint).

Figure 2 shows the percent (%) baseline PenH over time following treatment at equal nominal 5 mg doses of aqueous IpBr or aqueous TrCl. Each data point within the line represents the mean % baseline PenH of the treatment group (assessed as the peak PenH response from minutes 4-9 following Mch challenge at each timepoint). As shown in Fig. 2, the aqueous TrCl provided significantly more broncoprotection as compared to aqueous IpBr.

AIR Trospium Chloride Formulations Compared to Aqueous TrCl at Equal Doses (1 mcg)

Three powder TrCl formulations were produced for in vivo study as described in Examples 1 and 2. The three powder TrCl formulations were: 1) TrCl/Leu/DPPC (5/90/5); 2) TrCl/Leu/DPPC (5/85/10); and 3) TrCl/Leu/DSPC/DPPC (5/85/5/5). Guinea pigs were insufflated with aqueous TrCl or one of three powder TrCl formulations at an equal nominal dose of 1 mcg API. Bronchoprotection from Mch-induced bronchoconstriction was assessed at 2, 12, 16, 20, and 24 hours following TrCl treatment and compared to the pre-TrCl treatment baseline Mch response.

Figure 3 shows the percent (%) baseline PenH over time following treatment with aqueous TrCl or AIR-TrCl at a nominal dose of 1mcg API. Each line represents a group of animals treated with a single dose of TrCl. Each data point within the line represents the mean % baseline PenH of the entire treatment group (assessed as the peak PenH response from minutes 4-9 following Mch challenge at each timepoint. As shown in Figure 3, while all formulations provided broncoprotection, the dry powder TrCl formulations provided even greater protection as compared to the aqueous TrCl formulation.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.